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ORIGINAL ARTICLE

Prognostic factors for survival in amyotrophic lateral sclerosis patients treated with riluzole

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Abstract
The objective of this study was to identify prognostic factors for survival in amyotrophic lateral sclerosis from a large prospective observational study performed in France. The study included a cohort of 2069 patients fulfilling broad entry criteria treated with riluzole. Over 100 demographic, biological, clinical and quality-of-life variables were monitored and assessed for their effect on survival. Patients were randomized *post hoc* into two groups: one group (two-thirds of the patients) to generate the prognostic models and one group (one-third of the patients) to validate the resulting models. Thirteen variables were found to affect survival independently and were used to construct a survival prediction score, RL401. These included age, disease duration, slow vital capacity, intensity of tiredness (visual analogue scale), number of body levels with spasticity, atrophy and/or fasciculations, cough, distal muscle strength, household income, depression and two biological parameters, plasma creatinine levels and neutrophil counts. A simplified score, $RL401_S$, was constructed, designed to be easy to use and interpret. The predictive powers of the two scores were similar.

Key words: *amyotrophic lateral sclerosis, prognostic factors, survival analysis*

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons, characterized by a progressive muscle weakness leading to death. Mean survival time, commonly set at 3 years, is variable and ranges from 23 to 48 months with a 40% survival rate at 5 years in some studies (1). Long-term survivors (up to 20 years) have been authenticated by autopsy. This variability in the rate of progression makes it difficult to predict expected survival time for individual patients. This situation hampers the advance planning which is essential for therapeutic trials and for day-to-day management of ALS patients.

A number of studies has attempted to identify prognostic factors for disease progression in ALS (2–14). The most extensively documented are age, disease duration, diagnostic delay, site of onset and respiratory status. Based on a combination of these and other factors, scoring systems have been developed which attempt to predict survival expectancy (5,6,8). These scores had various limitations; for example, some were derived from a relatively small sample of patients, whereas others were based on historical data, raising the question of the quality of the data collected. In contrast, data collected during clinical trials, with a good quality of follow- up, generally did not reflect the overall ALS population due to the restrictive inclusion and exclusion criteria required for enrolment.

A large prospective open-label study of riluzole (15) using broad inclusion criteria provided an opportunity to collect data on survival and investigate potential prognostic factors. In particular, the French arm of this study involving a structured pharmacovigilance assessment (16) of over 2000 patients, collected over a hundred demographic, biological, clinical and quality-of-life variables at baseline that could be evaluated. The present report presents a retrospective analysis of the influence on survival of these factors and generates a survival score for predicting survival whose validity is assessed.

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Methods

Patients

The study included all eligible patients over the age of 18 years presenting clinical features compatible with a diagnosis of probable or definite ALS (17) with the exception of those with serum alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) levels over twice the upper limit of normal (ULN) at first visit, in whom riluzole is contra-indicated. After the inclusion visit, all patients received riluzole (50 mg b.i.d.). The intent-to-treat (ITT) population consisted of all patients enrolled who received at least one dose.

Data collection

Clinical examinations were carried out at inclusion and every three months. Standard clinical scales as well as 100 mm visual analogue scales (VAS) for cramps, stiffness, tiredness and fasciculations were used for clinical assessments as previously described (8). Additional clinical parameters monitored were reflexes, atrophy and spasticity. Forced and slow vital capacities were assessed at entry and every six months. Blood cell count, ALAT, ASAT and serum creatinine were assessed at inclusion and every three months.

Information was obtained regarding monthly income, financial aid and residential location. The COPING questionnaire was used to assess individual reactions to the illness (18) and the Sickness Impact Profile (SIP) (19) to evaluate the effect of the illness on physical and psychosocial aspects. Psychiatric comorbidity was assessed using the MADRS scale (20) and the MINI questionnaire (21). All these questionnaires were assessed at entry and every three months.

Survival time was defined as the duration between inclusion in the study and death.

Generation of prognostic scores

The study sample was divided into two groups, an analysis group used to generate the prognostic model and a validation group used to validate (*post hoc*) this model. Each patient was assigned a randomization number from a computer-generated list and attributed on this basis to either the analysis or validation group.

The initial prognostic score was derived through a two-step process inspired by the method proposed by Hosmer and Lemeshow (1989) (22). During the first phase, each variable was evaluated independently for its influence on survival using a Cox univariate model. Next, all variables with an initial p value of <0.2 in this first analysis were fed into a stepwise multivariate Cox proportional-hazards analysis. To be retained in this model, a variable was required to reach a significance threshold of $p<0.05$.

To generate the simplified score, all variables were recoded as categorical variables as described below. This was done in order to simplify the calculation of the score for potential users and to minimize the influence of measurement errors. Any variables where high proportions of missing data were observed were eliminated. This operation was performed in order to increase the reliability and stability of the measure and to ensure that the score could be calculated for as many patients as possible using only data systematically in the routine evaluation of ALS. In addition, any social variables that were culture-dependent (such as income) were eliminated to render the scale as independent as possible from potential cultural artefacts

Statistical analysis

Survival time was analysed using Kaplan-Meier curves. In the initial model, which included quantitative variables, the log linearity between the variable and survival was determined using a Cox model with two forced explicative variables (the variable and the variable squared). If log-linearity was rejected, the variable was re-coded, using quartile intervals in the first instance and adjustments to these intervals if necessary. In order to recode the quantitative variables as binomial categorical variables, we performed an iterative dichotomization of the data in order to identify the most sensitive cut-off point for predicting survival or non-survival in the model. In the simplified model, all variables were categorical and it was therefore unnecessary to assess log-linearity.

The prognostic factors identified by the multivariate Cox model were subsequently re-analysed in a Weibull model to identify those that were the most robust. This model, unlike the Cox model, does not make the assumption that the relative risk of survival is independent of time.

We used the following rules for attribution of missing data: missing data for a given variable representing less than 5% of the total population were replaced by the mean of that variable for the ITT population. If the missing data represented more than this value, a logistic model was used to study the relationship between the probability of the data being missing for individual prognostic factors and survival. Individuals were selected with the same profile for the variables retained in the preceding step, and the missing value was replaced by the median of that variable from the matched individuals. To include a sufficient number of patients, the number of variables required for a profile match was fixed at three.

To compare the match between the simplified categorical score and the intermediate score

obtained from the multivariate analysis, Akaike's criterion was used, since it takes into account both the likelihood of match and the number of parameters of the model, and thus determines the most adequate model in a cautious way.

Results

Patients

Overall, 2069 subjects were included in the study from June 1995 to June 1997, of whom 1398 were assigned to the analysis group and 671 to the validation group.

Demographic and clinical features of the total sample at baseline

Apart from age, gender, disease duration and El Escorial class, data were missing to different degrees (1–832 patients) for all the baseline variables. For the majority of variables, this concerned less than 15% of cases. The items with the most missing data were the psychiatric comorbidity measures (59% for both the MADRS and the MINI), vital capacity measurements (17%), COPING scores (68%) socioeconomic data (18%–36%), VAS scores (24%–25%) and, in particular, SIP quality of life scores (94%).

The demographic features of the 2069 patients included in the study are presented in Table I. With regard to symptoms, fasciculations (moderate or important) were present in the upper limbs (59.9% and 10.5%, respectively), the lower limbs (54.6% and 6.7%, respectively), the trunk (38.5% and 3.7%, respectively) and the tongue (40.8% and 8.3%, respectively). Atrophy was present in the upper limbs in 74% of the patients, in the lower limbs in 59% of the patients and in the tongue in 40% of the patients.

The mean manual muscle testing (MMT) score was 117.0 ± 27.2 points (maximum possible score: 150). The mean total bulbar functional score was 28.6 ± 11.1 (maximum possible score: 39) and the mean total limb functional score was 43.7 ± 16.6 (maximum possible score: 63). The mean VAS scores (maximum possible score: 100 mm) were: tiredness 55.1 ± 29.0, cramps 28.1 ± 25.8, stiffness 28.6 ± 29.0 and fasciculations 36.0 ± 27.1.

For technical reasons (difficulty or impossibility to blow), slow vital capacity (SVC) determination was only obtained for 92.7% of the patients (mean $\pm$ SD: 82.7 ± 27.6% of predicted values) and forced vital capacity (FVC) for 83.0% (mean $\pm$ SD: 83.1 ± 28.6%). Two hundred and twenty patients (10.6%) reported smoking and 204 of these quantified their consumption at an average of 13.4 cigarettes per day.

Monthly income varied between €762 and €3049 per month; 7.5% of patients declared receiving financial aid. Residence was equally divided between small urban, medium urban, large urban or rural areas. In the investigators' opinion, 42.0% of the patients understood their diagnosis and disease outcome.

Less than 40% of the patients replied to the whole of the Coping questionnaire and less than 10% the

Table I. Demographic data of the total, analysis and validation population at inclusion. Data are either given as mean $\pm$ SED (range) for age or as absolute values (%) for categorical variables and for missing data.

Parameter	Total population (n=2069)	Analysis population (n=1398)	Validation population (n=671)
Age (years)	62.3 $\pm$ 11.6 (23–88)	62.5 $\pm$ 11.8 (25–88)	61.7 $\pm$ 11.0 (23–87)
Missing data	None	None	None
Gender			
Male	1147 (55.4%)	777 (55.6%)	370 (55.1%)
Female	922 (44.6%)	621 (44.4%)	301 (44.9%)
Missing data	None	None	None
ALS diagnosis			
Probable	1012 (48.9%)	680 (48.6%)	332 (49.5)
Definite	1057 (51.1%)	718 (51.4%)	339 (50.5%)
Missing data	None	None	None
Disease onset			
Bulbar	628 (30.4)	445 (31.8)	183 (27.3)
Limb	1440 (69.6%)	953 (68.2%)	487 (72.6%)
Missing data	1 (0.05%)	None	1 (0.1%)
Disease duration			
<6 months	296 (14.3%)	203 (14.5%)	93 (13.9%)
6 months–2 years	1287 (62.2%)	887 (63.5%)	400 (59.6%)
2–5 years	470 (22.7%)	296 (21.2%)	174 (25.9%)
>5 years	15 (0.7%)	11 (0.8%)	4 (0.6%)
Missing data	1 (0.05%)	1 (0.1%)	None
Familial history of ALS			
Yes	84 (4.1)	53 (3.8)	31 (4.6)
No	1982 (95.8)	1343 (96.1)	639 (95.2)
Missing data	3 (0.1)	2 (0.1)	1 (0.1)

whole SIP questionnaire. On average, those who completed the Coping questionnaire were dealing with their illness neither well nor badly. The SIP questionnaire showed that the most affected activities were work (mean score $59.5 \pm 20.5/100$), household tasks (mean score $42.2 \pm 23.3/100$) and leisure activities ($37.0 \pm 20.8/100$) and the least affected were social life (mean score $18.7 \pm 14.4/100$), nutrition (mean score $19.2 \pm 12.9/100$) and awareness (mean score $21.6 \pm 17.7/100$). The mean MADRS score was 9.5 ± 8.5 on a scale of increasing severity of 0–60. In the MINI questionnaire, only 3.4% of the patients had suffered a major depressive episode, 4.7% had dysthymia and 3.3% general anxiety. Other psychiatric problems were observed with a frequency of $< 1\%$.

Haemoglobin and lymphocyte levels were low before treatment for 34.8% and 26.7% of the patients, respectively, while values for the other biological parameters tested were within normal limits in more than 85% of cases.

Survival

By the end of the study (date of final approval in France), 800 patients (38.7%) had died, the median survival time being 521 days (482–576, 95% CI) following inclusion into the study. The proportion of patients who died in the analysis (AG) and validation (VG) groups were respectively 39.1% and 37.9%, and the median survival time were respectively 521 days (477–576, 95% CI) and 522 days (CI: not assessable). The Kaplan-Meier survival curves for both groups were not significantly different (log rank, $p = 0.82$).

Prognostic factors

Over 100 demographic, clinical, biological and quality-of-life variables from the analysis population were tested individually as prognostic factors for survival. The principal of these are shown in Table II. Those that were most closely associated with survival ($p < 0.001$) were age, site of onset of disease, disease duration, presence of bulbar signs at inclusion, serum creatinine, blood platelets and neutrophils, number of regions with atrophy, presence of a brisk masseter reflex, fasciculations, distal muscle strength, most Norris bulbar and limb score items, VAS tiredness, slow and forced vital capacity and MADRS depression score.

Construction of the RL401s survival score

For the initial analysis using quantitative variables and all baseline variables, the stepwise sorting procedure of the multivariate Cox proportional hazard model identified 13 variables which affected survival independently. These variables were: age, disease duration, spasticity, fasciculations, atrophy, distal muscle strength, cough, VAS tiredness, slow vital capacity, MADRS score, household income, serum creatinine and neutrophil levels. These variables were all retained in a Weibull model which eliminates potential artefacts due to changes in associated risk over time.

All quantitative variables were then recoded as categorical variables. Disease duration and plasma creatinine were already coded as categorical variables in the initial analysis. Variables with high amounts of missing data, unlikely to be acquired in the course of standard follow-up of ALS patients by a neurologist, such as MADRS scores, household income or quality of life measures were also eliminated at this stage.

To generate the simplified model, the recoded variables were entered into the Cox multivariate model. Age $\leqslant 65$ years, disease duration > 2 years, slow vital capacity $> 80\%$ of expected values, creatinine > 60 μmol/l^{-1}, a low number of body regions with fasciculations or atrophy, distal muscle strength score > 56, atrophy, extensive spasticity or pyramidal signs, normal cough and good swallowing function were found to be statistically associated with survival. These variables were then entered into a Weibull model to generate the survival scale. A score

Table II. Principal variables entered into the univariate analysis. Those indicated in bold were significantly associated with survival ($p < 0.2$) and therefore entered into the multivariate analysis.

Demographics	Clinical variables	ALS history	ALS rating scales	Reflexes
Age	**Blood pressure**	**El Escorial criteria**	**MRC muscle score**	**Masseter reflex**
Gender	**Heart rate**	**Disease duration**	**Norris scale scores**	Hoffmann sign
Residence	**MADRS scale**	Family history	**VAS cramps**	Plantar reflex
	MINI subscales	**Site of onset**	**VAS tiredness**	
	COPING scales	**Bulbar signs**	VAS fasciculations	
		Knowledge of diagnosis	VAS stiffness	

Social factors	**Laboratory tests**	**ALS symptoms**	**Vital capacity**
Income	AST	**Atrophy**	**Slow VC**
Financial aid	ALT	**UMN involvement**	**Forced VC**
	Creatinine	Spasticity	**Smoker**
	Blood cell counts	**Fasciculations**	

Table III. Simplified ALS survival score: RL401s.

Variable	Scoring	Weight (s.e.)	Relative risk [95% CI]	*p*
1. Age	⩽65 years=1 >65 years=0	−0.483±0.090	0.617 [0.517,0.736]	0.0001
2. Disease duration	>2 years=1 <2 years=0	−0.784±0.122	0.456 [0.359,0.580]	0.0001
3. Plasma creatinine	>60 μM=1 ⩽60 μM=0	−0.252±0.099	0.777 [0.640,0.944]	0.0109
4. Atrophy	0/1 region=2 2 regions=1 3 regions=0	−0.217±0.073	0.805 [0.697,0.929]	0.0030
5. Pyramidal signs	0 region=3 1 region=2 2 region=1 3 regions=0	−0.120±0.049	0.887 [0.806,0.977]	0.0149
6. Spasticity	2 regions=2 1 regions=1 0 region=0	−0.225±0.072	0.799 [0.694,0.919]	0.0017
7. Fasciculations	0/1/2 regions=1 3 regions=0	−0.358±0.094	0.699 [0.582,0.841]	0.0001
8. Muscle strength	>56=1 ⩽56=0	−0.545±0.101	0.580 [0.476,0.706]	0.0001
9. Cough (Norris)	Normal=1 Abnormal/absent=0	−0.358±0.118	0.699 [0.554,0.881]	0.0024
10. Swallowing (Norris)	Normal=3 Soft food=2 Minced food=1 Semi-liquid food=0	−0.141±0.051	0.868 [0.785,0.960]	0.0059
11. Slow vital capacity	>80%=1 ⩽80%=0	−0.724±0.100	0.485 [0.399,0.590]	0.0001

on this scale could be calculated for each patient. This generated a relationship between the input baseline variables and score described by the following equation:

$$\begin{aligned} Score = {} & 0.483 \times 1I(age \leq 65 years) + 0.784 \times 1I \\ & (disease\ duration > 2 years) + 0.724 \times 1I \\ & (slow\ vital\ capacity > 80\%CeCa) + 0.252 \times 1I \\ & \left(creatinine\ level > 60 \mu mol/l^{-1}\right) + 0.358 \times 1I(0{,}1\ or \\ & 2\ levels\ with\ fasciculations) + 0.545 \times \\ & (1I(distal\ muscle\ strength\ score > 56) + 0.217 \times \\ & [1I(2\ levels\ with\ atrophy) + 2 \times 1I(0\ or\ 1\ level \\ & with\ atrophy)] + 0.225 \times [1I(1\ level\ with\ spasticity) \\ & + 2 \times 1I(2\ levels\ with\ spasticity)] + 0.120 \times [1I \\ & (2\ levels\ with\ pyramidal\ signs) + 2 \times 1I(1\ level\ with \\ & pyramidal\ signs) + 3 \times 1I(0\ level\ with\ pyramidal\ signs)] \\ & + 0.358 \times 1I(normal\ cough) + 0.141 \times [1I(swallowing \\ & \min ced\ food) + 2 \times 1I(swallowing\ soft\ food) + \\ & 3 \times 1I(swallowing\ normal\ food)] \end{aligned}$$

For the entire analysis population, the mean and median score were 2.5 with a range of 0.1–4.6 (Table IV). Nevertheless, the score was not normally distributed (p=0.0001). The relationship between the score (as a continuous variable) and survival was log-linear with a relative associated risk of 0.368 (Table IV), equivalent to a 60% decrease in the risk of dying per 1 unit increase. When the score was divided into 1-unit bins and displayed as Kaplan-Meier survival curves, these were hierarchical (Figure 1).

For example, in a patient aged 62 years with a disease duration of 2.5 years, with a slow vital capacity of 82%, a distal muscle strength score of 58, with no atrophy, pyramidal signs or fasciculations but one body region affected by spasticity, with a normal cough and eating soft food and a serum creatinine level of 56 μM, the score would be 4.56, and thus a good prognosis of survival.

Validation of of the RL401s survival score

Survival scores were then calculated for the 671 subjects in the validation group. Mean and median scores (2.5) were identical to those found previously in the analysis group (Table IV). Again, the relationship between the score and survival were log-linear, with an associated relative risk of 0.384 per unit score (Table IV), not significantly different from that observed in the analysis population. The relationship of the score with survival was log-linear when divided into bins (Figure 2).

Discussion

This study analysed a sample of 2069 ALS patients recruited within a period of two years.

Table IV. Distribution of RL401s scores in the analysis and validation populations.

	Analysis population $n=1398$	Validation population $n=671$
Test for normality (p)	0.21	0.0224
Mean ± SEM	2.5 ± 0.9	2.5 ± 0.9
Median (range)	2.5 (0.1–4.6)	2.5 (0.4–5.2)
Relative risk of survival per unit score [95% confidence intervals]	0.368 [0.331 – 0.409]	0.384 [0.330 – 0.447]
P	0.0001	0.0001

Standardization of treatment practice among the French ALS consortium ensured that patients were homogeneous in terms of associated treatment and methods of care. Inclusion criteria were large and 11.7 % of the patients were > 75 years, 0.7% had a disease duration of > 5 years and 30.3% a forced vital capacity < 60% of the expected value, these criteria being broader than those in previous large clinical trials (23–27). The cohort included approximately one-third of the entire French ALS population and should thus be representative of the overall ALS population with probable or definite ALS.

Missing data are a major pitfall when studying the determinants of survival in ALS patients. The reason for the large number of missing data is mainly in relation to the progressive difficulties that patients have in attending their planned visits. In our study, we paid great attention to managing missing data, since above a threshold of 5% bias may arise if data are not missing randomly. The hot-deck method we have used aimed to minimize potential bias and resulting distortion of distribution.

Another question was the incidence of riluzole on survival parameters. Since all patients received riluzole (50 mg b.i.d.), the effect of the drug on survival was identical with all patients. However, our study is not able to answer the question of the incidence of riluzole on potential prognostic factors. This study provides information only on prognostic factors for patients treated with riluzole. This issue has, however, been addressed in a recent analysis of prognostic factors for survival performed in a large historical database of 841 patients of whom 349 had received riluzole (Turner et al., 2002) (14). This demonstrated that riluzole was an independent prognostic factor which did not interact with any of the other identified prognostic variables (gender, El Escorial category, site of symptom onset, age of onset and time to diagnosis).

We tested the relation with survival of more than 100 parameters. When we designed this analysis, it appeared that the procedure of selection of the variables could raise some questions with regard to the stability and the possible extrapolation of the results. This uncertainty led us to perform two analyses: an exploratory analysis and a validation analysis. The latter demonstrated that the predictability of the score obtained after the exploratory analysis was satisfactory.

The first score, RL401, identified 13 independent prognostic variables with a significant effect on survival. The predictivity of this score was good when tested in the validation population. Of the 13 variables identified, age and disease duration have previously been shown to be strong predictive factors for survival. Three clinical variables, atrophy, spasticity and fasciculations, have a significant effect on survival. These variables appear to be indicators of the spatial extent of the disease and of the ratio of upper versus lower motor neuron involvement. Our results suggest that the risk of death increases with the number of regions with a lower motor neuron involvement but decreases when the upper motor neuron involvement increases. This suggests that there is a positive correlation between the degree and extent of upper motor neuron involvement and

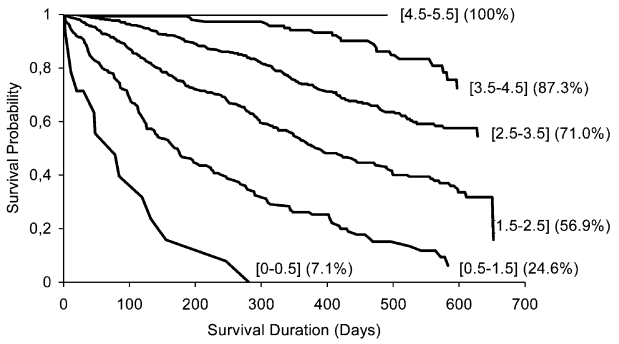

Figure 1. Kaplan-Meier survival curves according to $RL401_S$ score in the analysis population ($n=1398$). The unit bins into which the score was divided are indicated in the square brackets, and the percentage survival at the study end in round brackets.

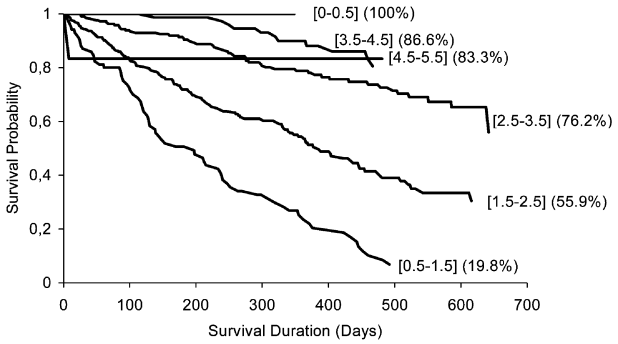

Figure 2. Kaplan-Meier survival curves according to $RL401_S$ score in the validation population ($n=671$). The unit bins into which the score was divided are indicated in the square brackets, and the percentage survival at the study end in round brackets.

survival. This positive relation between UMN involvement and survival was suggested in the riluzole phase III trial (Lacomblez et al., 1996) (8).

A previously undocumented biological variable, plasma serum creatinine, was identified during the analysis. Creatinine levels were below the normal range for 5.9 % of the patients. For these patients, this low value was a strong predictor of death. This number is far less than the number of patients with atrophy of limbs, suggesting that there is no clear relation between these two variables, and that this decrease is probably independent of muscle atrophy. We have no clear explanation for the relationship between a decrease in the creatinine levels and poor survival. Creatinine is a non-enzymatic breakdown product of creatine phosphate and its levels therefore are a direct reflection of the creatine pool that plays an important role in muscle metabolism. Dietary supplementation with creatine has been shown to prolong survival in a transgenic mouse model of ALS (Kliveny et al., 1999) (28) and a possible impact of creatine on cellular metabolism has been proposed to explain this effect. Our results would be compatible with such a hypothesis.

The $RL401_S$ score, based on RL401, contains simple categorical values to make it easy to handle in daily clinical practice. Although it contained fewer variables, the predictive power of $RL401_S$ was similar to RL401. We excluded from the $RL401_S$ score variables with a high probability of missing data, such as quality of life and psychiatric comorbidity, and restricted it to variables that are not sensitive to measurement errors. Eight out of the 11 variables can be evaluated by a simple examination of the patient, namely: age, disease duration, number of regions with atrophy, spasticity and fasciculations, and cough and swallowing. The distal muscle score is easily performed using the standardized MRC procedure. Two variables, creatinine levels and slow vital capacity are routinely performed. The $RL401_S$ score should therefore be practical for daily use in the clinic and useful for planning disease management in ALS.

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Appendix

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